RESPONSE

A. Status of the Claims

Claims 38, 47, and 49-60 were pending at the time of the Action. Claims 47 and 55-60 have been withdrawn.

B. Rejections Under 35 U.S.C. § 112

Claims 38 and 49-54 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Applicants traverse this rejection.

The present specification satisfies the enablement requirement because it teaches one of skill in the art how to make and use the claimed invention without undue experimentation. The Examiner does not dispute that a person of ordinary skill in the art could make an antigen fragment encompassed by the current claims. In fact, the Examiner acknowledges that the specification is enabling for immunogenic compositions comprising the recited antigenic fragments (Action, p. 3). The Examiner argues, however, that the specification is not enabling for vaccines because it is unpredictable that such antigen fragments would treat or prevent *H. pylori* infection (Action, p. 3).

In support of this rejection, the Examiner asserts that to enable a vaccine, the specification must present data demonstrating that the composition elicited a protective immune response against a pathogen challenge (Action dated 6/10/2008, p. 5 and 8). Applicants are not aware of any statute or case law that sets forth this standard of enablement. Rather, it is well known that to be enabling within the meaning of 35 U.S.C. § 112, the application must contain a description sufficient to enable one skilled in the art to make and use the claimed invention without unduly extensive experimentation. *In re Wands*, 858 F.2d 731, 736-737 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement).

Furthermore, demonstrating efficacy in human clinical trials is not a requirement for patentability. *In re Brana,* 51 F.3d 1560, 1568 (Fed. Cir. 1995). . "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." *Id.* The stage at which an invention in the pharmaceutical field becomes useful is well before it is ready to be administered to humans. *Id.*; *see also Ex parte Zavada*, Board of Patent Appeals and Interferences, Appeal No. 2001-1970 at page 10 ("First, we agree with Appellants that a therapeutic method need not be ready for clinical application in order to be enabled.") (non binding precedent).

The Examiner also emphasizes the ability to "predict" the outcome of the administration of the claimed vaccine (Action dated 6/10/2008, p. 5 and 8). While "predictability" may be one factor to consider when evaluating whether an amount of experimentation is undue, it is not a separate standard for determining compliance with the enablement requirement. In the *Wands* case, for example, someone could not have reasonably predicted which lymphocyte would produce a monoclonal antibody having the desired characteristics. Nevertheless, the Federal Circuit found the claims enabled because it was not undue experimentation to perform the process of immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics. *In re Wands*, 858 F.2d at 740.

Independent claim 38 is directed to a pharmaceutical composition comprising an isolated hyperimmune serum-reactive antigen fragment comprising an amino acid sequence encoded by a nucleic acid molecule fragment of SEQ ID NO:110 and comprising amino acids 4-37, 40-46, 52-57, 199-205, 222-229, 236-244, 250-267, 269-282, 27-197, 86-109, and/or 104-127 of SEQ ID NO:288. The pharmaceutical composition may be a vaccine. Significant in this regard, is that the antigen having the amino acid sequence of SEQ ID NO:288 was identified using sera from

individuals with antibodies against *H. pylori* (*see e.g.,* Specification, Example 3, and Table 1). In other words, this sequence was identified because of a demonstrated ability to stimulate an immune response in a subject. Moreover, the group of individuals with antibodies against *H. pylori* included both patients and ***healthy*** people (*see e.g.,* Specification, Example 1, p. 45-47). As can be seen in Table 3 of the specification, epitopes of the hyperimmune serum reactive antigen having the sequence of SEQ ID NO:288 were highly reactive with sera from ***both*** patients and healthy people. The presence of antibodies against *H. pylori* in the sera of healthy individuals suggests that these individuals were successful in raising a protective immune response against *H. pylori*. Accordingly, a person of skill in the art would have a reasonable expectation of success in using the currently claimed composition as a vaccine.

Additionally, on page 67, the specification discloses specific immunogenic epitopes within SEQ ID NO:288. The specification further teaches that hyperimmune serum reactive antigens or antigenic fragments thereof can be made by recombinant protein expression, in vitro translation, or peptide synthesis (Specification, page 15, first paragraph). The antigenicity of a particular sequence can be confirmed by seeing if it is bound by antibodies in sera from individuals with antibodies against *H. pylori* as described in Example 5 of the specification. The specification also discloses a pharmaceutical composition that is "a vaccine for preventing or treating an infection caused by *H. pylori* and/or other pathogens against which the antigens have been included in the vaccine." (Specification, page 38, fourth paragraph).

Accordingly, the specification teaches a person of ordinary skill in the art how to make and use the currently claimed pharmaceutical composition, including a vaccine, without undue experimentation. Applicants, therefore, request the withdrawal of this rejection.

C. Rejections Under 35 U.S.C. § 102

1. The Claims Are Novel Over Tomb

Claim 38 is rejected under 35 U.S.C. § 102(b) as being anticipated by Tomb. The Action asserts that Tomb teaches a hyperimmune serum-reactive antigen comprising SEQ ID NO:288. Applicants traverse.

The Action fails to establish a *prima facie* case of anticipation because the rejection is premised on a factual error. Contrary to the Action's assertion (*see* the sentence bridging p. 4-5), Tomb did not formulate the HP1341 polypeptide in a pharmaceutical composition. The heading of Table 2 in Tomb clearly states that the genes are listed with their ***putative identification***. It is also clear from reading Tomb that there no experiments were performed on any polypeptides encoded by the sequenced genes in order to determine their function. Accordingly, Tomb did not formulate the HP1341 polypeptide into any composition, much less a pharmaceutical composition.

Moreover, a claim cannot be anticipated by a reference if the allegedly anticipatory disclosure is not enabled. Mere naming or description of the subject matter is insufficient if it cannot be produced without undue experimentation. MPEP § 2121.01. Tomb does not anticipate the current claims because Tomb does not provide an enabling disclosure of the claimed ***pharmaceutical*** composition. Tomb describes a particularly large number of sequences, *i.e.*, the results of the whole genome sequencing of *Helicobacter pylori* strain 26695 including about 1.7 million base-pairs, which has been deposited in the NCBI Genbank with the accession AE000511.1. The disclosed full length HP1341 polypeptide (accession NP_208133.1) is one of the hypothetical proteins encoded by this complete genomic sequence and is described as a "siderophore-mediated iron transport protein." As noted above, this is a putative identification.

Tomb postulates that these sequences may be useful for drug discovery and vaccine development, but there is no data demonstrating such an effect or any guidance provided as to which sequences will be effective for these purposes and which will not. No further characterization, in particular no immunology-type of experiments have been done with the sequence. There is no discussion of SEQ ID NO:288 as a component of a pharmaceutical composition. Furthermore, the language in Tomb discussing vaccines and drug discovery is speculative, at best, and does not identify specific sequences for such purposes. *See* Tomb at page 539.

Tomb's guess that one or more of the sequences listed in the article may be useful in a pharmaceutical composition is not enabling as it would require undue experimentation to test ***all*** of these sequences, which encompass the entire genome of *H. pylori*, in the absence of any guidance as to which sequences would likely be immunogenic and thus useful in a pharmaceutical composition. Accordingly, the current claims are not anticipated by Tomb. Applicants request the withdrawal of this rejection.

2. The Claims Are Novel Over Legrain

Claims 38-46, 49, and 53-54 are rejected under 35 U.S.C. § 102(b) as being anticipated by Legrain (WO 02/066501), which is said to disclose fragments of SEQ ID NO: 288. Specifically, it is asserted that Legrain disclose amino acid sequences that are 100% identical to fragments of SEQ ID NO: 288.

As discussed above, a claim cannot be anticipated by a reference if the allegedly anticipatory disclosure is not enabled. Mere naming or description of the subject matter is insufficient if it cannot be produced without undue experimentation. MPEP § 2121.01; *see also Elan Pharms, Inc. v. Mayo Found. for Med. Educ. & Research*, 304 F.3d 1221, 1228 (Fed. Cir.

2002) (stating "The anticipating reference 'must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter.'").

Legrain does not anticipate the current claims because Legrain does not provide an enabling disclosure of the claimed composition. Legrain discloses about 1600 protein sequences from the Helicobacter genome identified by a yeast two hybrid system-based experimental setup, therefore having a domain for the putative role in protein-protein interactions ("SID"). Actual data was shown only for 96 of the SIDs (Table 5). Among the numerous SID domains presented, HPO406 with 119 amino acids was shown (SEQ ID NO:3186). Legrain did not appear to consider this particular fragment to be one of the best candidates to show in their protein-protein interaction-related experiments because the HPO406 is not disclosed on Table 5.

Legrain does not appear to provide any discussion concerning HPO406 nor does Legrain appear to disclose the use of HPO406 in a vaccine. In addition, Legrain did not show the immunogenicity and/or antigenicity of HPO406 or its subfragments. *See Elan Pharms, Inc.*, 304 F.3d at 1228 (stating "The anticipating reference 'must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter.'"). Thus, there is no data demonstrating that HPO406 may be used in a vaccine or any guidance provided as to which of the approximately 1600 sequences will be effective for this purpose and which will not. It would, therefore, require undue experimentation to test ***all*** of these sequences to determine which would be useful in a pharmaceutical composition.

Accordingly, the current claims are not anticipated by Legrain. Applicants request the withdrawal of this rejection.

3. The Claims Are Novel Over Kleanthous

The Action also rejects claims 38-46, 49-50, and 53-54 under 35 U.S.C. § 102(b) as being anticipated by Kleanthous (WO 98/43478), which is said to disclose SEQ ID NO: 288 as well as

fragments of SEQ ID NO: 288. The Action specifically cites Kleanthous' SEQ ID NOs: 118 and 228 as disclosing SEQ ID NO: 288 or a fragment thereof. In addition, Kleanthous is said to disclose that the antigen is immunoreactive with a monospecific hyperimmune antiserum. Applicants respectfully traverse.

Claim 38 recites that the antigen comprises "an amino acid sequence encoded by a nucleic acid molecule fragment of SEQ ID NO:110 ***and*** comprising amino acids 4-37, 40-46, 52-57, 199-205, 222-229, 236-244, 250-267, 269-282, 27-197, 86-109, and/or 104-127 of SEQ ID NO:288." While Applicants appreciate the Examiner providing sequence alignments in the current Action, these alignments do not contain an alignment of SEQ ID NO: 288 with Kleanthous' SEQ ID NO: 118. As Applicants' explained in their previous response, there is no significant homology between these two sequences. The Action, therefore, has not presented any evidence that Kleanthous' SEQ ID NO: 118 comprises amino acids 4-37, 40-46, 52-57, 199-205, 222-229, 236-244, 250-267, 269-282, 27-197, 86-109, and/or 104-127 of SEQ ID NO:288.

While Kleanthous' SEQ ID NO: 228 appears to be the same as SEQ ID NO: 288 in the present specification, Kleanthous does not anticipate the current claims because Kleanthous does not provide an enabling disclosure of the claimed pharmaceutical composition. *See* MPEP § 2121.01; *see also Elan Pharms, Inc.*, 304 F.3d at 1228; *Impax Laboratories, Inc.*, No. 2007-1513. Like the Tomb and Legrain references, Kleanthous describes a particularly large number of sequences, *i.e.*, the genomic sequence of a *Helicobacter pylori* strain in companion with about 700 predicted polypeptide sequences.

According to the real, wet-lab experiments described in the disclosure, six hypothetical ORFs were selected to be amplified by gene-specific primers. Kleanthous' GHPO 894 was ***not*** selected for such further study. Kleanthous postulates that these sequences may be useful in pharmaceutical formulations, but there is no data demonstrating this usefulness. In particular, no

further characterization steps directed to any of the putative protein compounds were found, and the immunoreactivity of the hypothetical polypeptides were mentioned just in theory without experimental data (page 60, line 10). Thus, the language in Kleanthous discussing vaccines and drug discovery is speculative, at best. Kleanthous also does not teach the particular fragments of SEQ ID NO:288 recited in claim 38. It would require undue experimentation to test all of these sequences in the absence of any guidance in the Kleanthous specification as to which sequences would likely be immunogenic and thus useful in a pharmaceutical composition.

For at least the reasons above, the current claims are not anticipated by Kleanthous. Applicants request the withdrawal of this rejection.

D. Rejections Under 35 U.S.C. § 103

Claims 50, 51, and 52 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kleanthous in view of Meinke (WO 02/059148). In particular, Meinke is cited as teaching adjuvants that are not disclosed by Kleanthous.

In making a determination as to whether a *prima facie* case of obviousness exists, the examiner should: (A) determine the "scope and content of the prior art;" (B) ascertain the "differences between the prior art and the claims at issue;" (C) determine "the level of ordinary skill in the pertinent art;" and (D) evaluate evidence of secondary considerations. *Graham v. John Deere*, 383 U.S. 1, 17 (1966); *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734; *see also MPEP* § 2141.

With regard to the scope and content of the prior art, the Office has failed to establish that the combination of Kleanthous and Meinke discloses or suggests every element of the rejected claims, namely a pharmaceutical composition comprising the specified fragments of SEQ ID NO:288. Applicants' claimed invention concerns "[a] pharmaceutical composition comprising an isolated hyperimmune serum-reactive antigen fragment comprising an amino acid sequence

encoded by a nucleic acid molecule fragment of SEQ ID NO:110 and comprising amino acids 4-37, 40-46, 52-57, 199-205, 222-229, 236-244, 250-267, 269-282, 27-197, 86-109, and/or 104-127 of SEQ ID NO:288." Claim 38. The pharmaceutical composition may further comprise an immunostimulatory substance. Claim 49. The immunostimulatory substance may be "a polycationic polymer, an immunostimulatory deoxynucleotide (ODN), a peptide containing at least two LysLeuLys motifs, a neuroactive compound, alum, or a Freund's complete or incomplete adjuvant." Claim 50.

Kleanthous is relied on as disclosing compositions that comprise *Helicobacter pylori* immunogenic antigens with a immunostimulatory substance. However, Kleanthous does not anticipate the current claims because Kleanthous does not provide an enabling disclosure of the claimed pharmaceutical composition. *See Impax Laboratories, Inc.*, No. 2007-1513. As discussed above, Kleanthous describes a particularly large number of sequences, *i.e.*, the genomic sequence of a *Helicobacter pylori* strain in companion with about 700 predicted polypeptide sequences. Kleanthous postulates that these sequences may be useful in pharmaceutical formulations, but there does not appear to be any data demonstrating this usefulness and the language discussing pharmaceutical formulations is speculative, at best. Kleanthous also does not teach the particular fragments of SEQ ID NO:288 recited in claim 38.

Meinke does not remedy the failure of Kleanthous to disclose a pharmaceutical composition comprising the specified fragments of SEQ ID NO:288. Meinke is cited only as disclosing immunostimulatory substances including polycationic polymer, an immunostimulatory deoxynucleotide (ODN), a peptide containing at least two LysLeuLys motifs, a neuroactive compound, and alum. Thus, the cited references, alone and in combination, fail to teach or suggest all of the elements of the independent claims, and thus they cannot render the claims obvious.

In view of the above, the current claims are non-obvious over the cited references. Applicants, therefore, request the withdrawal of these rejections.

E. Conclusion

Applicants believe this paper to be a full and complete response to the Office Action dated February 26, 2009. Applicants respectfully request favorable consideration of this case in view of the above comments and amendments.

Should the Examiner have any questions, comments, or suggestions relating to this case, the Examiner is invited to contact the undersigned Applicants' representative at (512) 536-5654.

Respectfully submitted,

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Date: October 21, 2009